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PATENT  
Attorney Docket No.: 010692-004532US

Commissioner for Patents  
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Alexandria, VA 22313-1450

On September 22, 2003

TOWNSEND and TOWNSEND and CREW LLP

By: Mark M. Martinek

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Stephen R. Gorfine

Application No.: Filed Herewith

Filed: Herewith

For: NITRIC OXIDE DONOR  
COMPOSITION AND METHOD FOR  
TREATMENT OF ANAL DISORDERS

Examiner: To be assigned

Art Unit: To be assigned

Declaration of Inventor Pursuant to MPEP  
§608.01(p) Regarding Sameness of  
Amendatory Material Previously  
Incorporated by Reference

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Stephen R. Gorfine, am the named and true inventor of the subject matter disclosed and claimed in the above-referenced patent application.

The references which are the source of the above amendatory material were incorporated by reference to exemplify the role and pathways by which "NO mediates the anorectal inhibitory reflex in animals and man." The above references each disclose L-arginine to be an important part of the pathway to NO formation and L-arginine in particular to be an NO precursor which releases NO under physiological treatment conditions.

I declare that the following recital of the Preliminary Amendment filed herewith sets forth amendatory material which consists of the same subject matter as that indicated to be incorporated by reference:

The role of nitric oxide in relaxation of the internal anal sphincter (IAS) in response to the rectoanal reflex has been studied in the opossum by others (see, Rattan S., Sarkar A., Chakder S., *Gastroenterology*, (1992 Jul), 103(1):43-50). They monitored resting pressures in the IAS using low-compliance continuously perfused catheters and reported the following.

L-NG-nitro-arginine (L-NNA), a NO-synthase inhibitor, caused significant dose-dependent suppression of the decrease in resting pressures in the IAS in response to the reflex mimicked by the rectal balloon distention. IAS relaxation in response not only to rectoanal reflex but also to other neural stimuli such as sacral nerve stimulation, local intramural stimulation, and the nicotinic ganglionic stimulant 1,1-dimethyl-4-phenylpiperazinium was also blocked by an NO-synthase inhibitor. The suppression of the neurally mediated IAS relaxation by L-NNA was stereoselective; D-NNA had no effect on the relaxation. The suppression of the rectoanal reflex-induced IAS relaxation by L-NNA was completely reversed by NO precursor L-arginine stereoselectively as D-arginine failed to reverse the suppressed IAS relaxation. The decrease in the resting pressure of the IAS caused by sodium nitroprusside was modified neither by the neurotoxin tetrodotoxin nor by L-NNA. Furthermore, the inhibitor of NO synthase did not modify the decrease in the resting pressure of the IAS by the direct-acting beta-adrenoceptor agonist isoproterenol. It was concluded that NO or a NO-like substance is an important mediator of IAS relaxation in response to noradrenergic, noncholinergic nerve stimulation.

Another study by others on the release of nitric oxide by activation of nonadrenergic noncholinergic neurons of internal anal sphincter has also been reported (see, Chakder S., Rattan S., *Am J. Physiol*, (1993 Jan), 264(1 Pt 1):G7-12.). This study investigated the direct release of nitric oxide (NO) in response to the stimulation of nonadrenergic noncholinergic (NANC) nerves. Isolated smooth muscle strips of the opossum (*Didelphis virginiana*) internal anal sphincter (IAS) were used. This study reported the following:

Electrical field stimulation (EFS) of these strips using the appropriate parameters was reported to cause a frequency-dependent fall in the resting tone of the IAS. The chemiluminescence method was used in the study to measure the release of NO. The stimulation of NANC neurons by the nicotinic stimulant 1,1-dimethyl-4-phenylpiperazinium (DMPP) and EFS caused IAS relaxation with an accompanying release of NO. The study found pretreatment of the smooth muscles

with the neurotoxin tetrodotoxin and the NO-synthase inhibitor NG-nitro-L-arginine (L-NNA) abolished the release of NO and the fall in the resting tension of IAS in response to lower frequencies of EFS and DMPP. Addition of the NO precursor L-arginine reversed to control levels of the loss of the release of NO and the IAS relaxation in the presence of L-NNA. Again, the effect of L-NNA and L-arginine on NO release and IAS relaxation was stereoselective. D-NNA and D-arginine had no significant effect. The release of NO from IAS smooth muscle strips caused by vasoactive intestinal polypeptide was also abolished by L-NNA. However, both isoproterenol and atrial natriuretic factor caused IAS relaxation without any increase in NO release. These investigations show that NO is directly released in response to the stimulation of gut NANC inhibitory neurons.

An additional study of nerve mediated relaxation of the human internal anal sphincter investigated the role of nitric oxide. See, O'Kelly T., Brading A., Mortensen N., Gut, (1993 May) 34(5):689-93. This reference concerns whether nitric oxide (NO) is the non-adrenergic, non-cholinergic neurotransmitter which is released by enteric inhibitory nerves to mediate relaxation of the human internal anal sphincter. Isolated muscle strips were mounted in a superfusion organ bath so as to record their isometric tension. This study reported the following:

An exogenous donor of NO, sodium nitroprusside, relaxed the strips in a dose dependent manner. In the presence of atropine and guanethidine, transmural field stimulation produced relaxations. These relaxations were sensitive to tetrodotoxin. These relaxations were also inhibited in a concentration dependent and stereospecific manner by antagonists of NO synthase; completely by L-nitroarginine and partially by L-N-monomethyl arginine. These inhibitory effects were reversed by L-arginine. D-arginine did not reverse them. The relaxations were abolished by the nitric oxide scavenger, oxyhaemoglobin, but not methaemoglobin. The O'Kelly, et al. findings strongly indicated that NO is, or is very closely associated with, the non-adrenergic, non-cholinergic neurotransmitter which mediates the neurogenic relaxation of the human internal anal sphincter.

The subject matter of the above recitals closely correspond to the Abstracts for each of the above cited references. The recitals have in particular been amended to make it clear that the inventors are not describing their own work. True copies of each of the Abstracts for the above cited references are enclosed as Exhibits

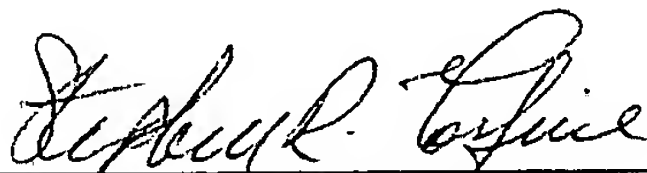
A, B, and C, respectfully. A true copy of the earliest priority document (i.e., the specification of U.S. Patent No. U.S. Application No. 08/250,555, filed on May 27, 1994) is also enclosed as Exhibit D. This document incorporates the above cited references in the first paragraph of p. 5. This application is a continuation application of the co-pending U.S. Patent Application No. 10/021,168 (Exhibit E) which recites the above references at p. 5, lines 3-10, and incorporates them by reference at p. 9, lines 1-3.

In view of the foregoing, I declare and respectfully submit that the above recited amendatory material belongs to the same material incorporated by reference in the referencing application.

I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Date: 9/12/03

  
Stephen R. Gorfine

# COPY

## DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled NITRIC OXIDE DONOR COMPOSITION AND METHOD FOR TREATMENT OF ANAL DISORDERS, the specification of which is attached hereto.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed: NONE

I hereby claim the benefit under Title 35, United States Code, 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application: U.S. Application Serial No. 08/250,555, filed May 27, 1994 and entitled "A Pharmacological Preparation for the Treatment of Anal Disorders".

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and to file and prosecute any corresponding foreign applications, including any international applications under the Patent Cooperation Treaty or the European Patent Convention: J. David Wharton, Reg. No. 25,717; Don M. Bradley, Reg. No. 22,412; Michael B. Hurd, Reg. No. 32,241; Joan Optican Herman, Reg. No. 31,968; Patrick A. Lujin, Reg. No. 35,260; Michael J. Gross, Reg. No. 35,528; and L. Bartley Eppenauer, Reg. No. 35,499, telephone number (816) 474-6550. Address all correspondence to: SHOOK, HARDY & BACON P.C., One Kansas City Place, 1200 Main Street, Kansas City, Missouri 64105-2118.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor's signature:

Stephen R. Gorfine, MD 1/5/95  
Stephen R. Gorfine Date

Residence: New York county, New York  
Citizenship: United States of America  
Post Office Address: 1215 Fifth Avenue  
New York, New York 10029



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PTO/SB/81 (02-01)


Approved for use through 10/31/2002. OMB 0651-0035

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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<b>POWER OF ATTORNEY OR AUTHORIZATION OF AGENT</b>	<b>Applicati n Number</b>	10/021,168
	<b>Filing Date</b>	December 11, 2001
	<b>First Named Inventor</b>	Stephen R. Gorfine
	<b>Title</b>	NITRIC OXIDE DONOR COMPOSITION AND METHOD FOR TREATMENT OF ANAL DISORDERS
	<b>Group Art Unit</b>	Not yet assigned
	<b>Examiner Name</b>	Not yet assigned
	<b>Attorney Docket Number</b>	010692-004531US

I hereby appoint:

☒ Practitioners at Customer Number **20350** → 

OR

☐ Practitioner(s) named below:

Name	Registration Number
	20350

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

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☒ The above-mentioned Customer Number.

OR

☐ Practitioners at Customer Number →

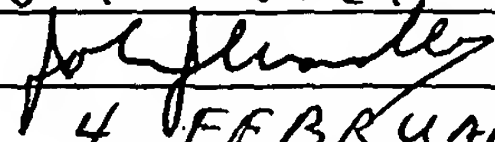
<input type="checkbox"/> Firm or Individual Name				
Address				
Address				
City		State		ZIP
Country				
Telephone		Fax		

I am the:

☐ Applicant/Inventor.

☒ Assignee of record of the entire interest. See 37 CFR 3.71.  
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

**SIGNATURE of Applicant or Assignee of Record**

Name	JOHN J. CHANDLER
Signature	
Date	4 FEBRUARY 2002

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below\*.

☒ \*Total of 1 forms are submitted.

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PTO/SB/96 (08-00)  
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Attorney Docket No. 010692-004531US

## STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Stephen R. Gorfine

Application No./Patent No.: 10/021,168

Filed/Issue Date: December 11, 2001

Entitled: NITRIC OXIDE DONOR COMPOSITION AND METHOD FOR TREATMENT OF ANAL DISORDERS

Cellegy Pharmaceuticals, Inc., a corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of an undivided part interest

in the patent application/patent identified above by virtue of either:

- A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the Patent and Trademark Office at Reel       , Frame       , or for which a copy thereof is attached.

OR

- B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: Stephen R. Gorfine To: Neptune Pharmaceutical Corporation  
The document was recorded in the United States Patent and Trademark Office at  
Reel 7374, Frame 0516, or for which a copy thereof is attached.

2. From: Neptune Pharmaceutical Corporation To: Cellegy Pharmaceuticals, Inc.  
The document was recorded in the United States Patent and Trademark Office at  
Reel 9052, Frame 0861, or for which a copy thereof is attached.

3. From:        To:         
The document was recorded in the United States Patent and Trademark Office at  
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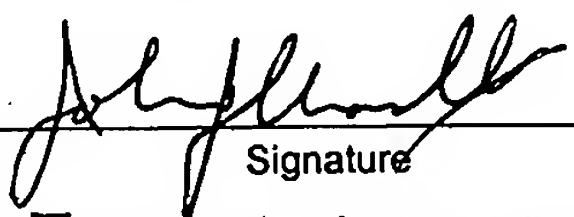
☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ Copies of assignments or other documents in the chain of title are attached.

[NOTE: A separate copy (i.e., the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.8]

The undersigned (whose title is supplied below) is empowered to sign this statement on behalf of the assignee.

4 FEBRUARY 2002  
Date

  
Signature  
JOHN J. CHANDLER  
Typed or printed name

VP CORPORATE DEVELOPMENT  
Title

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Washington, D.C. 20231  
00452045

MAY 27, 1998

PTAS  
TOWNSEND AND TOWNSEND AND CREW LLP  
MARGARET A. POWERS  
TWO EMBARCADERO CENTER, 8TH FLOOR  
SAN FRANCISCO, CA 94111-3834



\*100676211A\*

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SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 03/27/1998

REEL/FRAME: 9052/0861  
NUMBER OF PAGES: 6

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

NEPTUNE PHARMACEUTICAL CORPORATION

DOC DATE: 12/31/1997

ASSIGNEE:

CELLEGY PHARMACEUTICALS, INC.  
1065 EAST HILLSDALE BOULEVARD, SUITE 418  
FOSTER CITY, CALIFORNIA 94404

SERIAL NUMBER: 08970447  
PATENT NUMBER:

FILING DATE: 11/14/1997  
ISSUE DATE:

SERIAL NUMBER: 08250555  
PATENT NUMBER: 5504117

FILING DATE: 05/27/1994  
ISSUE DATE: 04/02/1996

SERIAL NUMBER: 08666264  
PATENT NUMBER: 5693676

FILING DATE: 06/20/1996  
ISSUE DATE: 12/02/1997

9052/0861 PAGE 2

MAYA BENNETT, EXAMINER  
ASSIGNMENT DIVISION  
OFFICE OF PUBLIC RECORDS

04-07-1998



Attorney Docket No. 010692-0045301

FORM PTO-1595  
(Rev. 6-93)

100676211

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To the Honorable Asst. Commissioner for Patents. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Neptune Pharmaceutical Corporation

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

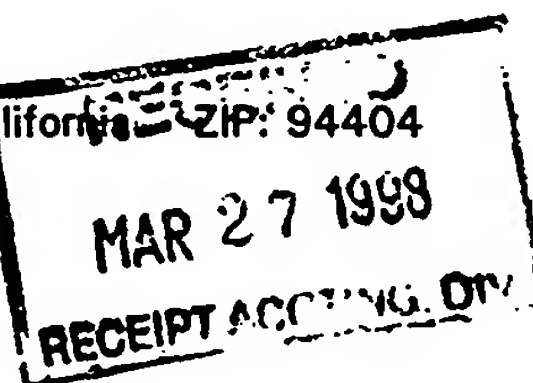
2. Name and address of receiving party(ies):

Name: Cellegy Pharmaceuticals, Inc.

Internal Address:

Street Address: 1065 East Hillsdale Boulevard, Suite 418

City: Foster City State: California ZIP: 94404



Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger  
☐ Security Agreement ☐ Change of Name  
☐ Other:

Execution Date: December 31, 1997

4. Application number(s) or patent number(s).

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s) 08/970,447

B. Patent No.(s) 5,504,117

Additional numbers attached? ☒ Yes ☐ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Margaret A. Powers  
TOWNSEND and TOWNSEND and CREW LLP  
Two Embarcadero Center, 8th Floor  
San Francisco, California 94111-3834  
(650) 326-2400

6. Total number of applications and patents involved:

7. Total fee (37 CFR 3.41):..... \$ 120.00

- ☐ Enclosed ☒ Charge Fees to Deposit Account  
☒ Charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to deposit account

8. Deposit account number: 20-1430

04/06/1998 SSHITH 00000090 201430 08970447  
01 FO:581 40.00 CH  
02 FO:581 80.00 CH

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Margaret A. Powers  
Name of Person Signing

Signature

March 23, 1998  
Date

Atty. Reg. No. 39,804

Total number of pages including cover sheet, attachments, and document:

10. Change Correspondence Address to that of Part 5? ☒ Yes ☐ No

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(Continued from Page 1)

2. Additional name(s) and address(es) of receiving party(ies):  
(Continued from Page 1)

4. Additional application number(s) or patent number(s):  
(Continued from Page 1)

A. Patent Application No.(s)

B. Patent No.(s)

5,693,676

## PATENT ASSIGNMENT

For good and valuable consideration, the receipt of which is hereby acknowledged, the person(s) named below (referred to as "ASSIGNOR" whether singular or plural) has sold, assigned, and transferred and does hereby sell, assign, and transfer to Cellegy Pharmaceuticals, Inc., a California corporation, having a place of business at 1065 East Hillsdale Boulevard, Suite 418, Foster City, CA 94404 ("ASSIGNEE"), for itself and its successors, transferees, and assignees, the entire worldwide right, title, and interest in all inventions and improvements ("SUBJECT MATTER") that are disclosed in United States Letters Patent listed on Schedule A attached hereto and the patent applications listed on Schedule B attached hereto, together with any reissue, extension, improvement, division, continuation or continuation-in-part of any thereof, in the U.S. or worldwide, and all rights of priority resulting from the filing in the United States of the patents or patent applications identified on Schedule A or B.

ASSIGNOR agrees that ASSIGNEE may apply for and receive patents for SUBJECT MATTER in ASSIGNEE's own name.

ASSIGNOR agrees to do the following, when requested, and without further consideration, in order to carry out the intent of this Assignment: (1) execute all oaths, assignments, powers of attorney, applications, and other papers necessary or desirable to fully secure to ASSIGNEE the rights, titles and interests herein conveyed; (2) communicate to ASSIGNEE all known facts relating to the SUBJECT MATTER; and (3) generally do all lawful acts that ASSIGNEE shall reasonably consider desirable for vesting in ASSIGNEE the rights, titles, and interests herein conveyed. ASSIGNOR further agrees to provide any successor, assign, or legal representative of ASSIGNEE with the benefits and assistance provided to ASSIGNEE hereunder.

ASSIGNOR represents that ASSIGNOR has the rights, titles, and interests to convey as set forth herein, and covenants with ASSIGNEE that ASSIGNOR has made or will make hereafter no assignment, grant, mortgage, license, or other agreement affecting the rights, titles, and interests herein conveyed.

This Assignment may be executed in one or more counterparts, each of which shall be deemed an original and all of which may be taken together as one and the same Assignment.

Name and Signature

Date of  
Signature

Date Declaration  
Executed By This Person

Neptuna Pharmaceutical Corporation

By Stephen R. Lawrence, MD  
[ASSIGNOR NAME]  
Stephen R. Lawrence, MD

31 984  
December 30, 1997

31 987  
December 30, 1997

**SCHEDULE A**

**Patents**

<b><u>Country</u></b>	<b><u>Patent No.</u></b>	<b><u>Date of Patent</u></b>	<b><u>Title</u></b>
<b>U.S.A.</b>	<b>5,504,117</b>	<b>4/2/96</b>	<b>Pharmacologic Preparation for the Treatment of Anal Disorders</b>
<b>U.S.A.</b>	<b>5,693,676</b>	<b>12/2/97</b>	<b>Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders</b>



# **SCHEDULE B**

## **Patent Applications**

<b><u>Country</u></b>	<b><u>Serial/App. No.</u></b>	<b><u>Filing Date</u></b>	<b><u>Title</u></b>
Israel	113,448	4/20/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
China	95190687.9	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
Korea	700442/1996	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
Mexico	960386	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
Singapore	9600491-6	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
Canada	2168247	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
Japan	500835/96	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
EPC	95916264.5	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
U.S.A.	08/970,447	11/14/97	Nitric Oxide Donor Composition for Treatment of Anal Disorders

Callego-Neptune Asset Purchase Agreement

State of New York  
County of New York

On December 31, 1997 before me, \_\_\_\_\_ personally  
appeared Stephen R. Gortine personally known to me or proved to me on the basis  
of satisfactory evidence to be the person whose name is subscribed to the within instrument and  
acknowledged to me that (he/she) executed the same in [his/her] authorized capacity, and that by  
[his/her] signature on the instrument the person, or the entity upon behalf of which the person  
acted, executed the instrument.

Mina L. Kuscsik  
Notary

Notary Seal  
MINA L. KUSCSIK  
Notary Public, State of New York  
No. 4602348  
Qualified in Suffolk County JAN 31, 1999  
Commission Expires \_\_\_\_\_

